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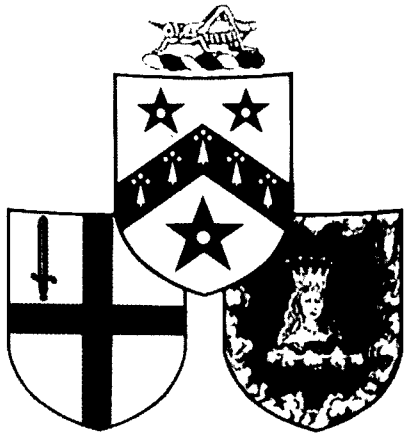

EXPLORING THE BRAIN

Lecture 6

DRUGS AGAINST MENTAL ILLNESS

by

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6 March 1996

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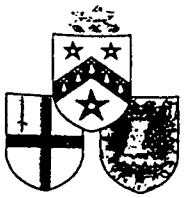

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SUSAN GREENFIELD: *GRESHAM LECTURE 6*

Drugs against Mental Illness

Neurons communicate using chemicals, the release of a 'transmitter', from one brain cell on to the next. By modifying how these transmitters are made in the brain, their availability, the molecular target of their action, or indeed their removal, therapeutic drugs can combat a diverse range of brain disorders.

Although it might seem straightforward to design drugs that target a particular transmitter system in the brain and hence 'cure' a disorder, we shall see the situation is far more complex in that there is not a simple one to one matching of one transmitter to one disorder. Rather, as we shall see, one transmitter usually participates in more than one disorder and most disorders can be influenced by more than one transmitter system. Moreover, rather than using a knowledge of brain chemistry to develop drugs, it is more the case that serendipitous use of drugs has taught us about brain chemistry. Some of the most effective treatments of brain disorders have been discovered by sheer accident.

For example, some 50 years ago it was discovered that a drug used to treat tuberculosis, 'iproniazid', produced the unexpected effect of making the patients euphoric. At about the same time, a completely

different drug, reserpine, was being given for hypertension: although it was very effective at lowering blood pressure, the patients ended up virtually suicidal. Hence although iproniazid and reserpine were being given for totally different conditions, they appeared to be linked regarding an important side effect. One (iproniazid) elevated mood, whereas the other (reserpine) depressed it. This antithetical action on mood turned out to be mirrored in the biochemical action of these two drugs. Iproniazid increased the availability of an important class of transmitters (the aminos) whereas reserpine depleted the brain of these chemicals. Hence the 'amine hypothesis' of depression was formulated: depression was attributed to a lack of availability of brain amines, most particularly serotonin and noradrenaline.

Soon antidepressant drugs were developed that prevented the breakdown of noradrenaline or serotonin. Although these agents did indeed prove effective, a further riddle still remained. Although the drugs would have increased the amine supply within one or two days, the therapeutic effect was not apparent after some ten days. This lag between increased amine availability and actual anti-depressant effect showed that something else had to happen in the brain before the patients' mood was changed. Clearly, we cannot extrapolate from a simple increase in a certain class of transmitters directly to a complex event like a shift in one's state of mind. Nonetheless, the drug rationale first prompted by reserpine and iproniazid, persists today in the treatment of depression. The highly popular Prozac works via an action on serotonin in the brain.

Another chance observation that was to transform the lives of many occurred in the last half of the nineteenth century. The eminent French neurologist Charcot used to hold regular salons at his home in Paris. As was the custom of the day, many of the fashionable women attending enhanced their natural assets by applying a chemical into their eye which dilated the pupil, and hence rendered them, they hoped, more attractive. This drug (atropine) is in fact a blocker of a sub-type of the molecular target for a particular transmitter, acetylcholine. Atropine was known at the time as 'Bella Donna' (lovely lady), after its cosmetic effect of making the facial expression seemingly loving and tender. However, these female participants at Charcot's salon complained that Bella Donna had an unpleasant side effect of making the mouth rather dry. Nowadays this observation would come as no surprise since it is well established that acetylcholine also normally allows the mouth to remain moist by producing saliva.

Charcot was at that time concerned with some patients he was treating who were suffering from a disease referred to originally as the shaking palsy, but renamed by him after the physician who first described the condition in 1817, James Parkinson. Parkinson's disease is characterised by tremor, muscle rigidity and difficulty in moving. A less well known feature of the disease is that sufferers quite frequently are subject to uncontrolled dribbling at the mouth. Charcot's idea was very simple and aimed at rather modestly tackling the dribbling in Parkinson's disease: administer Bell Donna to his patients.

Needless to say, Charcot would never have anticipated the effects of his treatment. Surprisingly, the Bella Donna not only reduced the amount of dribbling, but much more importantly, the disorders of movement were improved!

Parkinson's disease is due to the slow loss of a particular group of neurons in the brain that use not acetylcholine, but a totally different chemical messenger, dopamine. It seems strange therefore that a condition resulting from loss of these dopamine cells should be alleviated by a drug (atropine) which acts instead on the efficacy of acetylcholine. The answer lies in the fact that transmitter systems in the brain *interact.* The neurons using dopamine make direct contact with other cells in the front of the brain, in an area known as the 'striatum'. These striatal cells use acetylcholine and normally work as a kind of see-saw, in perfect balance with the dopamine cells.

However, when the dopamine cells are compromised, as in Parkinson's disease, then the see-saw springs out of balance and the acetylcholine cells in the striatum become too powerful. By blocking the action of acetylcholine with atropine, the previous balance between dopamine and acetylcholine cells is at least partly restored. After Charcot's discovery, anti-acetylcholine drugs were subsequently given as a treatment for Parkinson's disease until the 1960s, when an improved therapy was developed, of L-DOPA. L-DOPA is the chemical from which the brain makes dopamine. By taking L-DOPA therefore, a Parkinsonian patient is replenishing as directly as possible the depleted

levels of dopamine in their brain, caused by the death of certain neurons. From this story we can learn that it is not the case that in the body there is one transmitter for one function, and vice verse. Rather, we have seen an example of one transmitter (acetylcholine) affecting more than one function (dribbling and movement); but we can also see more than one transmitter (acetylcholine and dopamine) contributing to a single function (movement).

The see-saw between the brain area containing the dopamine cells (the substantia nigra) and that containing the acetylcholine cells (the striatum) can also be seen as central in another brain disorder, Huntington's chorea. Huntington's Chorea is characterised by wild, involuntary movements giving the impression of a grotesque caricature of dancing (hence the name 'chorea', from the Greek for 'dance'). In Huntington's chorea, blockers of dopamine are effective, whilst agents such as L-DOPA would make the condition even worse. Generally, any drug that makes Parkinson's disease better such as Bella Donna/atropine, makes Huntington's disease worse and vice versa.

Let us look at a completely different brain disorder where interaction of transmitters is again a very important consideration. Schizophrenia is a complex disorder of thought and perception. Literally from the Greek, a 'split mind', it is a disorder of thought commonly presenting initially in young people and affecting 1% of the population over 20 years of age. Symptoms can be divided into 'positive' and 'negative'. Positive symptoms include: delusions, hallucinations,

incoherence, motionless 'catatonic' behaviour, inappropriate response to a particular situation (such as laughing at a funeral). Negative features include: unchanging facial expression, lack of expressive gestures, poverty of speech, slowness in replying, lack of energy, inability to form friends, absence of feelings of enjoyment.

As yet the immediate underlying cause or causes of schizophrenia are not known. There is no discrete site in the brain that appears to be consistently damaged, as in Parkinson's disease. However, *post mortem* schizophrenic brains frequently show that the symmetrical cavities towards the front of the brain (lateral ventricles) are enlarged with an accompanying shrinkage of the surrounding structures, (hippocampus and cortex).

There is a genetic component to schizophrenia, but the hereditary factor is only one factor in the final manifestation of the disease. For many years schizophrenia was associated with dopamine systems: drugs like Largactil (classified as 'neuroleptics'), which block the molecular target (receptors) for dopamine, were known to combat many of the key symptoms of thought and perceptual disorders. Moreover a drug that potentiated dopamine systems (amphetamine) frequently gave rise to schizophrenia-like symptoms, such as paranoia. It was thought originally therefore that schizophrenia was attributable basically to an excess of dopamine.

However there are two basic problems with this 'dopamine hypothesis'. First, even though neuroleptic drugs work within hours to block dopamine receptors, the therapeutic effects of these drugs will not be apparent for several weeks. It must be the case therefore that the action of the drug is triggering longer term changes within the cell that will not be immediately apparent. However there is a second problem: there is no consistent finding of high levels of dopamine *post mortem* in schizophrenic brains.

A plausible explanation for this idea is that, again, there is a transmitter interaction so that an imbalance occurs. We can imagine dopamine being in a form of equilibrium with another transmitter, just as we saw for dopamine and acetylcholine in the substantia nigra and striatum. Perhaps then schizophrenia would be no more attributable to an 'excess' of dopamine any more than Parkinson's disease was attributable to an 'excess' of acetylcholine. Unlike in Parkinson's disease however the site of the dysfunction in schizophrenia is not known. However there are several transmitters that could be implicated.

Another candidate transmitter is acetylcholine, since chemicals relating to the manufacture of this chemical are significantly higher in certain regions of schizophrenic brains *post mortem*. Moreover, it is known that yet another group of neurons, this time containing the transmitter glutamate, impinge on the same neuronal target (in a part of the striatum) as does a certain group of dopamine cells implicated in schizophrenia. This group of dopamine cells is particularly implicated in

schizophrenia since it seems to be the area where neuroleptics selective for a sub-type of dopamine receptor, will preferentially bind.

One final example of a contributing transmitter is serotonin, which is in a further group of neurons making contact with regions rich in dopamine. The hallucinatory drug LSD, which modifies serotonergic systems, produces similar perceptual disorders to schizophrenia. It has been used experimentally as a model for schizophrenia. In any event, although no one as yet knows the entire neurochemical basis of schizophrenia, it is clearly more complex than a mere excess of dopamine. Since there is no 'magic bullet' responsible for schizophrenia, it would be unreasonable to expect that a successful anti-schizophrenia drug could be developed that targets only one transmitter system. The treatment of choice to date, the neuroleptics, are should be viewed as tranquillisers rather than as selective agents 'curing' schizophrenia specifically.

Just as dopamine is important in more than one disorder (schizophrenia and Parkinson's disease), so another widespread transmitter in the brain plays a fundamental role in two very different disorders: epilepsy and anxiety. Epilepsy is characterised by convulsions whilst anxiety has no direct physical manifestations and is thought of more as an unwanted and unenjoyable attitude to outside events. It goes without saying, that epilepsy and anxiety are very different, but both are most usually treated by drugs with *essentially the same net action,*

facilitation of another transmitter, gamma amino butyric acid (GABA). Some anticonvulsant drugs (barbiturates and benzodiazapines) act on the GABA receptor in different ways too enhance normal GABA transmission, whist others (sodium valproate) may also facilitate GABA synthesis by inhibiting the enzyme that normally breaks it down.

But such knowledge of how drugs work at the biochemical level is not sufficient to extrapolate the mechanism of their therapeutic value. There is not a direct, exclusive and sufficient causal link between anxiety and low GABA levels: low GABA levels can also be associated with epilepsy, so obviously other determining factors must be involved. From these observations, it should also be apparent by now that we certainly will not be able to identify a single 'function' for GABA.

GABA changes the distribution of ions inside the neuron so that the generation of action potentials, the electrical signal of the neuron, is less likely. For this reason, GABA is frequently referred to as an 'inhibitory' transmitter. But how might we relate this inhibition at the cellular level to epilepsy and anxiety? Intuitively it is tempting to view an inhibitory transmitter like GABA as inhibiting otherwise unfettered and undesirable phenomena, be they epileptic fits, or wave upon wave of worries and anxieties. But what physical entity within the brain, in each case, would the GABA actually be inhibiting? The problem is that other factors must be taken into account, such as the particular brain region affected, and the relation of that brain region to other regions.

Let us return to Huntington's chorea, where there is a loss of GABA-containing neurons in the striatum. There would be many neuronal contacts between the degenerating cell in this tragic disease, and the final neuron in the spinal cord that controls, or otherwise, the spontaneously contracting muscle. Therefore, there can be no simple connection between the loss of 'inhibition' normally exerted by GABA and loss of motor control observed in patients with Huntington's Chorea. We need only to imagine an inhibitory inter- connection that is in turn inhibited by GABA to see that the eventual effect could actually be one of excitation.

In conclusion then, just as one dysfunction is influenced by many transmitters, so any one transmitter participates in more than one function or dysfunction. Frequently these functions and dysfunctions seem to bear no relation to each other, and often seem almost antithetical. There is thus no 'obvious' drug strategy for any one disorder. Moreover, any action of a drug at the cellular level cannot in itself explain its corresponding action at the therapeutic, behavioural level. On the other hand, the actions of drugs might provide us with a very valuable strategy for understanding the physical factors contributing to, and hence the physiological basis of, the mind.